論文 / 著書情報
Article / Book Information

題目(和文)	高分子鉄キレーターを用いた腫瘍微小環境における不安定鉄調節機構の解明とその癌治療への応用
Title(English)	Investigation of Labile Iron-Modulation in Tumor Microenvironment Using Polymeric Iron Chelators and Its Utility for Cancer Therapies
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種別(和文)	論文要旨
Type(English)	Summary

（博士課程）
Doctoral Program

論 文 要 旨

THESIS SUMMARY

系・コース： Department of, Graduate major in	ライフエンジニアリング	系 コース	申請学位（専攻分野）： Academic Degree Requested	博士 Doctor of	（ 学術 ）
学生氏名： Student's Name	Guo Haochen		審査員主査： Chief Examiner	西山伸宏	

要旨（英文 800 語程度）
Thesis Summary（approx.800 English Words ）

1. Introduction

Iron is an essential nutrient for cells, and it is involved in several important cellular processes such as redox and hemoglobin synthesis, etc. Recent studies showed that excess labile iron in the tumor microenvironment (TME) contributes to abnormal tumor metabolism, facilitating tumor growth and drug resistance. In such a case, depletion of tumoral iron using iron chelators could block the iron utilization of the tumor and achieve cancer treatment. Despite efforts with small molecular iron chelators such as deferoxamine (DFO), the antitumor efficacy of tumor iron depletion remains limited due to rapid blood clearance and low tumor accumulation. Meanwhile, the absence of an iron chelator with high tumor accumulation has impeded the study to indicate the role of excess labile iron in TME formation. In this regard, our laboratory recently developed a poly(ethylene glycol)-poly(aspartic acid) conjugated with multiple DFO molecules, which exhibits prolonged blood circulation and higher tumor accumulation than free DFO. Here, by the use of the DFO-polymer conjugate termed PDFO, this research investigated the effect of labile iron modulation on TME and designed combination therapies incorporating PDFO for enhanced cancer therapy, indicating the promise of PDFO in tumor treatment.

2. Research Content

1) Excess extracellular labile iron ions have been reported to protect tumor cells from oxidative damage by decomposing H_2O_2 via the Fenton reaction, hence limiting the therapeutic effect of oxidative drugs, such as high-dose vitamin C (VC). Herein, I indicated that intravenously injected PDFO could inactivate the extracellular labile iron ions in the target tumor and control tumor-associated redox, thus enhancing the in vivo antitumor activity of the high-dose VC by augmenting the generation of VC-induced H_2O_2.

In the *in vitro* experiments, both free DFO and PDFO effectively enhanced the cytotoxicity of VC against murine and human colon cancer cells. This effect was achieved by promoting the generation of H_2O_2 in the cell culture medium containing labile iron. In the *in vivo* experiments, intravenously injected PDFO improved the therapeutic effect of high-dose VC. In contrast, free DFO did not exhibit the same enhancement in the subcutaneous tumor models. The results of this research underscore the significance of targeting tumor-associated iron ions in high-dose VC therapy and emphasize the role of extracellular iron in the TME.

2) 5-Aminolevulinic acid (5-ALA) can be converted into protoporphyrin IX (PpIX) in many cancer cells, which exerts phototoxicity upon photoirradiation and achieves photodynamic therapy (PDT) against cancer. However, tumoral iron compromises the PDT effect of 5-ALA by promoting the metabolization of PpIX to the non-phototoxic heme. In this study, I developed the combination therapy of PDFO and 5-ALA and demonstrated that PDFO significantly improved the effect of 5-ALA-induced PDT in a subcutaneous tumor model by boosting the 5-ALA-induced intracellular PpIX.

The results demonstrated that free DFO significantly enhanced PpIX accumulation levels and augmented PDT effects by depleting intracellular labile iron while PDFO moderately improved these effects in cultured cancer cells. However, in vivo studies revealed that PDFO significantly enhanced PDT effects, whereas free DFO did not. This suggests the importance of delivering iron chelators to target tumors and highlights the promising potential of PDFO in combination with 5-ALA PDT. Additionally, these results unveiled the iron modulation mechanism of PDFO in the TME, providing a promising strategy for intracellular iron depletion and its implications in cancer treatment.

3) Recent studies revealed that excess tumoral iron might inactivate antitumor immune cells and promote the infiltration of immunosuppressive cells in a tumor, inducing the immune escape and limiting the immune checkpoint inhibitor represented immunotherapy. To investigate how excess tumoral iron affects antitumor response, I intravenously injected PDFO into a tumor model with immunosuppressive TME and examined its effect on antitumor immune response.

The results in this research demonstrated that PDFO could be taken by macrophages rather than tumor cells both in vitro and in vivo, leading to an increase in macrophage iron levels and the upregulation of pro-inflammation markers. Moreover, I found that the intravenous administration of PDFO enhanced the antitumor efficacy of anti-PD-L1 antibody by increasing T cell-dependent antitumor immune response. PDFO augmented tumor infiltration of Th1 in immunotherapy and suppressed the immune checkpoint blockage-induced Treg proliferation. These efforts indicate the potential of iron homeostasis manipulation in enhanced antitumor immune response and present a promising strategy to improve clinical outcomes for cancer patients undergoing immunotherapy. Additionally, this research highlights the importance of intercellular iron homeostasis in tumor-infiltrated immune cell interaction, underscoring the need for further investigation into the role of iron in cancer immunology.

3. Conclusion

In this research, I demonstrated the effect of labile iron modulation on antioxidants, PDT resistance, and immunosuppression in TME using PDFO, revealing the potential of PDFO for improving existing therapies. These findings provide insights into the complex interaction between iron and cancer, which contributes to further investigation and therapeutic development.